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Long term antibiotic therapy may be an effective treatment for children co-morbid with Lyme disease and Autism Spectrum Disorder

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ABSTRACT

Patients diagnosed with Lyme disease share many of the same physical manifestations as those diagnosed with an Autism Spectrum Disorder (ASD). In this study four male children (ages 26–55 months) who have an ASD diagnosis and one male child (age 18 months) who displayed behaviors consistent with an ASD, were assessed using the SCERTS Assessment Process Observation (SAP-O) form. The SAP-O meets state and federal requirements for providing a comprehensive, ongoing assessment of a child with an ASD [33]. The SAP-O form measures children's abilities using observational, authentic assessment procedures in the domains of joint attention, symbol use, mutual regulation, and self regulation via observations of specific behaviors in familiar settings [33]. The five children tested positive for Lyme disease and their SAP-O score was evaluated before and after 6 months of antibiotic therapy. Each child was prescribed 200 mg of amoxicillin three times per day and three of the five children were prescribed an additional 50 mg of Azithromycin once per day. All of the children's scores on the SAP-O assessment improved after 6 months of antibiotic therapy. The assessors also reported anecdotal data of improved speech, eye contact, sleep behaviors, and a reduction of repetitive behaviors.

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Introduction

Autism is a developmental disorder that appears in the first 3 years of life; a physical condition linked to abnormal biology and chemistry that affects the brain's normal development of social and communication skills [30]. Over the last 20 years the prevalence of Autism has increased by over 600% [6]. Because of current prevalence rates, the term Autism Spectrum Disorders (ASD) is commonly used. This classification (ASD) is inclusive of diagnoses under the Pervasive Developmental Disorders in the Diagnostic and Statistical Manual IV-TR: including Autistic Disorder, Aspergers Disorder, and Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS) [12]. Many hypotheses for increased prevalence rates have been proposed, this study investigates the correlation between ASD and Lyme disease and the use of long term antibiotics as a possible treatment.

Lyme disease is a multisystemic illness caused by the spirochete bacteria *Borrelia burgdorferi* (Bb); it is the most common vector born disease in the United States [13]. Lyme disease has been called "The Great Imitator" because infected individuals often present neurological and physical symptoms that are similar to other disorders [8]. Late stage Lyme disease is commonly misdiagnosed because it mimics many better known disorders [32].

Misdiagnosis of initial symptoms of Lyme disease and delayed treatment can lead to debilitating chronic illnesses with musculoskeletal, cognitive, and neuropsychiatric impairments [10]. Children who have gone undiagnosed and later been found to have Lyme disease have displayed one or more of the following symptoms: decreased reading comprehension and handwriting skills, impaired speech fluency, attention deficit behavior, hyperactivity, withdrawal from activities with peers, inability to perform at grade level, obsessive compulsive behavior, anxiety, mood swings, dyslexic-like behaviors, sensitivity to light and sound, and inability to manage frustration [2,21]. All of these symptoms would be considered criteria for Autism Disorder [4].

A review of case studies and literature has shown that between 3% and 25% of children reportedly lose their ASD diagnosis and enter the normal range of cognitive, adaptive and social skills [23]. The question should be raised, why do a small percentage of children diagnosed with an ASD lose their diagnosis and what caused them to present behaviors similar to an ASD? Or were these children misdiagnosed with an ASD and do the behaviors they present have a physiological, pathogen induced cause?

Published studies in peer reviewed literature have shown that a number of individuals who are diagnosed with an ASD test positive

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for Lyme disease. A study of was conducted by Dr. Garth Nicolson in 2003 where 20% of the children diagnosed with an ASD came back positive for Lyme disease [9]. A similar study was conducted by Dr. Aristo Vojdani [38] and 22% of the ASD patients he tested came back positive. Also, in a personal interview with an assistant of Dr. Charles Ray Jones, the only pediatric physician in the world who exclusively treats Lyme disease, he estimated that 50% of his patients who have been diagnosed with an ASD have come back positive for Lyme disease (Personal Interview April 8, 2011).

Hypothesis

The hypothesis proposed is that there may be a correlation between Lyme disease and ASDs and that long term antibiotic therapy may be an effective treatment. The theory is based on peer reviewed literature comparing biological similarities suggesting a casual comorbility, geographical rates of prevalence in the United States for Lyme disease and ASD, and a small sample set of children whose autistic symptoms improved when prescribed oral antibiotics (amoxicillin and in some cases combined with Azithromycin). The children in the study were selected when the lead author inquired to their parents about testing their child for Lyme disease. There has been published text suggesting an association between Lyme disease and ASDs [9], but a study of how children diagnosed with Lyme disease and an ASD react to antibiotics could not be found in a search of peer reviewed literature. Published studies have demonstrated that patients diagnosed with Lyme disease that have cognitive impairments, specifically memory, and fatigue improved with long term antibiotic therapy, but relapsed when they were taken off the antibiotic [17]. When the five children in the study tested positive for Lyme disease the question of whether or not their autistic symptomology would improve when antibiotic therapy began. Four of the five children had previously received a diagnosis of Autism Disorder and one of the five presented symptoms suggesting an ASD. All five children tested positive for Lyme disease, via positive Indirect Fluorescent Antibody (IFA), Western Blot assay, and clinical diagnosis. Some of the symptoms that the parents reported that led to the clinical diagnosis was that their child was lethargic, frequently displayed flu-like symptoms, sleep disturbance, irritability, attention issues, obsessive behavior, speech impediments, light or sound sensitivity, and their mother tested positive for Lyme disease (Fig. 1). The children also live in an area that is considered endemic for Lyme disease. It is not clear if Lyme disease was the causative factor in the children's ASD diagnosis or if Lyme disease is simply exasperating the autistic symptoms in the children, but in this vey limited study the children's autistic behaviors quantitatively improved on an ASD assessment tool when treated with long term antibiotics.

Antibiotic therapy is the recommended treatment for patients diagnosed with Lyme disease [13], but the duration of the antibiotics needed to properly treat the patient has been debated by researchers [36]. The children's physician determined a treatment of long term antibiotics was the best course of treatment to treat the children's infection.

If the hypothesis is validated, through further research, the impact could be significant. It is very rare for a pediatrician to screen for Lyme disease when a patient displays behaviors suggesting an ASD. If a long term course of antibiotics can help individuals diagnosed with an ASD and Lyme disease better assimilate to the environment around, via increased verbal communication skills and increased social interaction, their chances of becoming an independent productive member of society could possibly increase.

Evaluation of the hypothesis

Making a correlation between Lyme disease and ASDs is critical for validating the use of antibiotics as a potential treatment method for individuals who display autistic behaviors and Lyme disease is suspected. It should be noted that the decision to treat the children in the study with antibiotics was based on the physician's decision to care for Lyme disease, not autistic behavior.

The subsequent information is not quantified and only presents an informal correlation of geographic parallel and physical symptoms presented in Lyme disease and ASD patients, but the similarities are what led to screening the children in the study for Lyme disease.

Lyme disease and autism: a statistical increase

Over the last 20 years the number of individuals diagnosed with an ASD and those diagnosed with Lyme disease have increased [14] [37]. The fact that the disorder and the disease have increased during the same time period does not necessarily mean they are related, there are many other factors that could contribute to the increase of diagnoses of ASD. Upon examining geographic representations of rates of Lyme disease and cross referencing those with prevalence rates of ASD diagnoses by geographic region, there are some compelling correlations between the two. Populations of

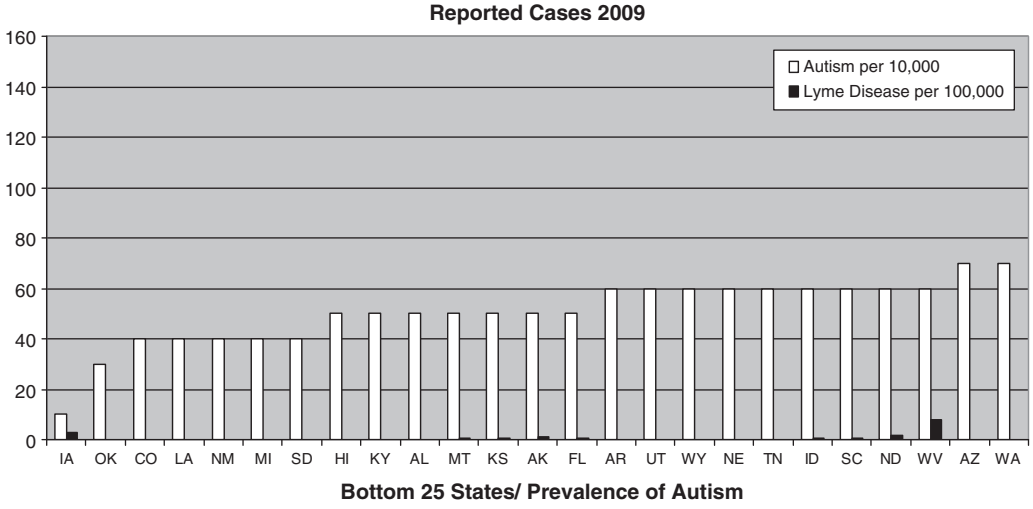

Fig. 1. Bottom twenty-five states for prevalence of Autism Disorder and prevalence of Lyme disease in those states in 2009 [14,37].

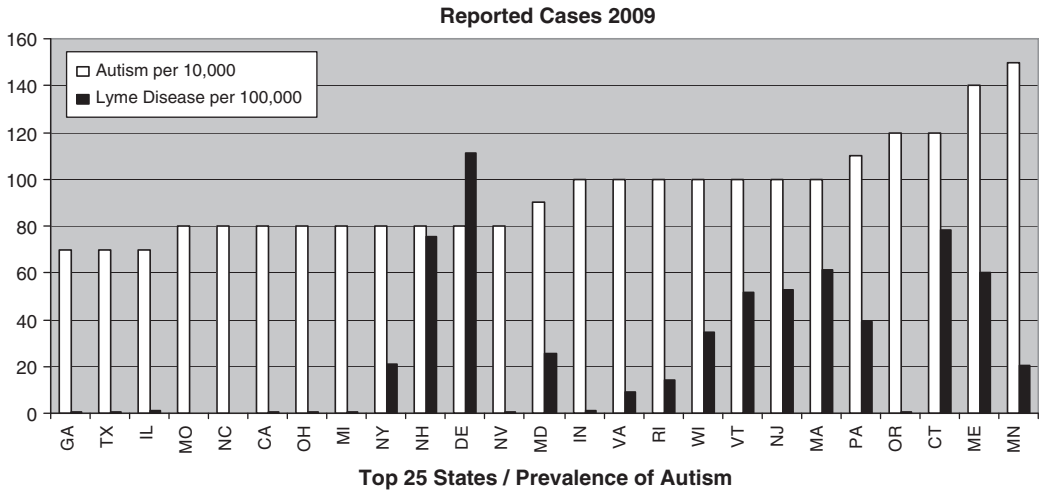

Fig. 2. Top twenty-five states for prevalence of Autism Disorder and prevalence of Lyme disease in those states in 2009 [14,37].

infected ticks are predominantly found in north eastern and upper mid west regions of the United States [11] and these correspond to areas with higher rates of ASD diagnoses [37].

Of the twenty states that reported the highest occurrence of Autistic Disorder (a specific ASD) per 10,000 people; fifteen reported a higher than average number of Lyme disease cases (Fig. 2). Conversely, of the twenty states that reported the lowest incidence of Autistic Disorder per 10,000 people; zero reported a higher than average number of Lyme disease cases (Fig. 1). The average number of reported individuals with Lyme disease per state per 100,000 people in 2009 was 13.69 [14].

Autism and Lyme disease: similar biological abnormalities

At present time the origin of ASD's are largely unknown although genetic, environmental, immunological, and neurological factors are thought to play prevalence in the rates of ASDs [6]. Over the last decade medical researchers have struggled to fully understand the genetic abnormalities in children with ASDs.

One biological abnormality that ASDs have been linked to is autoimmune disorders [5]. An autoimmune disorder is a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue [29]. Currently, there is no known cause of autoimmune disorders [3] but, patients with Lyme disease who do not respond to initial antibiotic treatment and present physical and neurological symptoms can attribute the continuing symptoms to persistent infection or pathogen-induced autoimmunity [1]. The National Institute of Allergy and Infectious Diseases [28] claims:

> "Antibodies against the OspA epitopes of *B. burgdorferi* have been shown to cross react with neural tissue. Such antigenic mimicry may have the potential to generate autoimmune inflammatory reactions that could be responsible for the neurological symptoms associated with chronic Lyme disease".

This suggestion that some autoimmune disorders have an active infectious disease component could provide a link between Lyme disease and a number of patients diagnosed with an ASD. In published studies, the immune history of families affected by an ASD was compared to the immune history of a control group consisting of families with no history of an ASD diagnosis. The prevalence rate of autoimmune disorders was greater in families with a history of ASDs as compared to the control group. Further, as the number of autoimmune disorders increased from one to three, the prevalence of ASD was also greater [15].

Another irregularity those diagnosed with Lyme disease and an ASD share is hypoperfusion. Hypoperfusion occurs when there is decreased blood flow through an organ; if prolonged, it may result in permanent cellular dysfunction [16].

A study examined the SPECT scans of thirteen individuals who had a diagnosis of Lyme disease. The SPECT scans showed multiple areas of hypoperfusion in the temporal lobes of the patients [25]. Some of the patients in the study were diagnosed with anxiety and depression. When those individuals began antibiotic treatment they showed improvements in their neuropsychiatric symptoms and the areas of hypoperfusion decreased [25].

Another study comparing children with an ASD to those with intellectual disabilities found significant hypoperfusion in the temporal lobes of children diagnosed with an ASD, particularly in the left and right superior temporal gyrus [39]. There was no hypoperfusion found in the comparison group of individuals affected by intellectual disabilities [39].

Kolb & Wishaw [24] have identified eight principle symptoms of temporal lobe damage: (1) disturbance of auditory sensation and perception, (2) disturbance of selective attention of auditory and visual input, (3) disorders of visual perception, (4) impaired organization and categorization of verbal material, (5) disturbance of language comprehension, (6) impaired long-term memory, (7) altered personality and affective behavior, (8) altered sexual behavior. Nearly all of the symptoms of temporal lobe damage listed by Kolb & Wishaw [24] could be identified as criteria for several specific diagnoses consistent with an ASD using criteria diagnoses under Pervasive Developmental Disorders in the DSM-IV-TR. Damage to the temporal lobe can also have effects on an individual's personality. Further, temporal lobe epilepsy can cause perseverative behavior and speech, paranoia, and aggressive rages [7]. Blumer and Benson's [7] identification of perseverative behaviors in individuals with temporal lobe injury certainly is aligned with those frequently observed in individuals diagnosed with an ASD.

Perseverative behaviors are defined as "continual involuntary repetition of a mental act usually exhibited by speech or by some other form of overt behavior" [27]. One aspect of the diagnostic criterion for Autistic Disorder is stereotyped and repetitive use of language or idiosyncratic language or echolalia [4]. Other behaviors, listed as diagnostic criterion for Autistic Disorder, that are similar to Kolb & Wishaw's and Bummer & Benson's behavior due to a damaged temporal lobe are: delay in, or total lack of, the development of spoken language, apparently inflexible adherence to specific, nonfunctional routines or rituals, and lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level [4].

Further investigations have been conducted between the relationship of hypoperfusion in the brain and its effects on the severity of an individual's autistic symptoms [20]. In the study a brain analysis was performed on forty-five children diagnosed with Autism Disorder. As part of that study, the level of hypoperfusion via brain analysis was compared to the score on the Autism Diagnostic Interview-Revised (ADI-R). In comparing the score on the ADI-R, a negative correlation pattern emerged. When the scores on the ADI-R were lower, the rate of hypoperfusion was more prevalent, suggesting that temporal hypoperfusion is related to the severity of the individual's autistic behavior [20].

Empirical data: case studies of five children diagnosed with an ASD (Or ASD like behavior) and Lyme disease and their measurable progress before and after antibiotics

Four children who have a diagnosis of an ASD and one who displayed behaviors consistent with an ASD were assessed using the SCERTS-SAP Observation [SAP-O] form before and after 6 months of antibiotic therapy. The SAP-O form profile summary consists of 62 observable behaviors under the joint attention domain, fifty behaviors under the symbol use domain, forty behaviors under the mutual regulation domain, and 56 behaviors under the self-regulation domain (Fig. 3). The children were observed by their teacher and their parents in a setting that was familiar to the child. After the observation they assigned a numerical score to the child's behavior. If the child did not display the assessed behavior during the observation period parents and teachers assigned a value based on typical behavior observed on a day to day basis. The lead author, who has graduate level training in ASD assessment, was available to all of the parents and teachers if they needed any clarification on the assessment. The SAP-O score of the five children was evaluated before and after 6 months of antibiotic therapy. The combined mean score of both the parents and the teachers were calculated in an attempt to yield more valid results.

All of the children had at least 8 months of early intervention services before antibiotic therapy began. The teachers of the five children each reported minimal or no gains in the child's ability to communicate verbally or initiate bids for social interaction during the pre-antibiotic period (Personal communication March 5, 2011). All of the children in the study had different teachers, but each teacher reported using the Applied Behavior Analysis (ABA) approach. ABA uses methods derived from scientifically established principles of behavior and incorporates all of the factors identified by the US National Research Council as characteristic of effective interventions in educational and treatment programs for children who have Autism [19].

Additional data were collected from the parents of the five children including physical symptoms, positive bands on the child's Western Blot IgM and IgG, co-infections, and age of diagnosis ASD and LD (Fig. 13).

It should be noted that all five children continued antibiotic therapy after the 6 month period of observation, by request of their physician. No other children were screened or included in the study. One child is not officially diagnosed with an ASD, but displayed many characteristics aligned with those consistent with a diagnosis of ASD while receiving special education services for "general developmental delays." Specifically, the behaviors demonstrated that are consistent with ASD include: delayed speech, little to no eye contact, restrictive and repetitive behaviors, and sensory sensitivities.

Child A

As of 4/15/2011 Child A is 3 years, 10 months old. The parents reported a normal child birth with no complications. They also reported fairly typical development for the first 18 months of life. Child A displayed reciprocal interaction with parents at 3 months, displayed emotions in proper context at 6 months, said his first word and responded to simple commands at 12 months, and walked at 12 months. All of these milestones fall under typical social, language, and motor skill development of typical developing children in the first year of life [31].

Child A initially developed verbal communication from age 12 months to 18 months when he independently spoke 15 words. At 18 months the parents reported a difference in his demeanor. They reported that Child A's language regressed from fifteen words to just a few words, that he frequently repeated, to a complete loss of spoken words at 20 months. The parents also reported that he frequently became dysregulated, most noticeably when his routine changed (personal communication, March 1, 2011).

After the initial regression of spoken words Child A did not speak for 14 months. In that time period the parents had him diagnosed at the University of Iowa. The doctors gave Child A a diagnosis of PDD-NOS at age 26 months. Following the suggestions from the team at the University the parents had him enrolled in Early Intervention Services. Child A received in home instruction from a trained professional who used the ABA approach.

One of Child A's goals in his Individual Education Plan (IEP) was to increase verbal communication. Child A was presented with vocabulary picture cards that had the 95 nouns listed on the Dolch most frequently used noun word list. The picture card was held close to the teacher's mouth and the name of the noun on the card was said while Child A sat across from the table. The 95 cards were

Examples of behaviors assessed on the SAP – O Model

Joint Attention
Initiates bids for attention, engages in extended reciprocal interaction

Symbol Use
Spontaneously imitates familiar actions or words immediately after a model, responds to own name, and understands a variety of names without contextual cues

Mutual Regulation
Shares negative and positive emotion attunes to changes in partners' expression of emotion, requests help when frustrated

Self Regulation
Initiates bids for interaction, participates in new and changing situations, and independently decreases intensity of dysregulated state.

Fig. 3. Examples of behaviors included, by not limited to, in the SCERTS SAO form. Parents and teachers gave a score of 2, 1, or 0 on 214 behaviors. Scoring Key: 2 = criterion met consistently 1 = criterion met inconsistently 0 = criterion not met based on observed or reported information or would not be expected.

presented to Child A nearly every day for 8 months, but Child A did not speak any words during the work sessions or any other time in that 8 month period (personal communication March 1, 2011).

Child A was diagnosed with Lyme disease in April of 2010; he began taking the antibiotic amoxicillin three times a day at that time. After 14 months of not speaking any words (Age 20–34 months) Child A spoke his first word, post regression, after ten days of being on the antibiotic. The teachers and parents continued to present the vocabulary picture cards and they reported a steady increase in Child A's verbal identification (Fig. 4).

If the increased verbal communication that Child A displayed was by virtue of the antibiotic therapy these findings could be significant since delay, or total lack of, the development of spoken language is one of the diagnostic criteria of Autism Disorder [4]. During the 6 month period of assessment both the parents and teachers claimed that the only intervention that changed in Child A's routine was the use of antibiotics, he still received Early Intervention services and the team used the same ABA approach that they did before he began treatment for his Lyme disease.

At the time of publication of this paper Child A is still taking antibiotics. Teachers and parents of Child A reported that he continues to show positive progress, but he still meets the criteria for an ASD (Fig. 5).

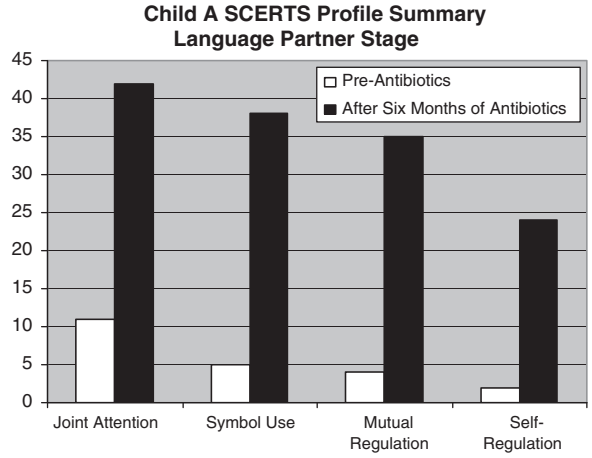

Fig. 5. SCERTS profile summary scores for Child A before antibiotic therapy began and 6 months into antibiotic therapy.

Child B

As of 4/15/2011 Child B is 4 years and 6 months old. The parents reported a normal child birth with no complications. Early in life Child B achieved many typical developmental milestones; he smiled and gave consistent eye contact at 1 month, smiled when given a positive antecedent at 3 months, sat up at 4 months, recognized himself in the mirror at 6 months, crawled at 8 months, and walked at 8 months. All of these milestones fall under typical social, language, and motor skill development of typical developing children in the first year of life [30]. The parents became concerned about Child B's development when he began toe walking and hand flapping, refused to eat certain foods, displayed no signs of pretend play, stopped interacting with peers, and had not displayed any form of verbal communication around the age of 18 months. At age 30 months Child B was formally diagnosed with PDD-NOS at the University of Iowa. He began special education pre-school shortly after he was diagnosed. His teachers use an ABA approach (personal communication January 18, 2011).

The parents of child B were very concerned that he did not follow instructions and that he was not engaged in activities with adults and peers. They asked Child B's teachers to design a work session to help him follow one word prompts with the goal of him eventually completing independent activities. One of the work sessions the teachers designed was to have Child B sit at his table and point to various items around the room when he was prompted verbally. The teacher would say "Child B look at the lamp," they would then wait 5 s and observe if he would look or point at the item. If he did not respond after 5 s they gave him a second verbal prompt and pointed to the item themselves. A positive response was credited when Child B's eye gaze followed the point or when he pointed to the object. The teachers would repeat this activity with five items per work session. Before Child B began antibiotics his eye gaze almost never followed the teacher's point. But after antibiotic therapy began he followed the teachers point over 80% of the time (Figs. 6 and 7).

If the increased joint attention that Child B displayed was a result of the antibiotic therapy these findings could be significant since a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people is one of the diagnostic criteria of Autism Disorder [4].

The parents and teachers of Child B were interviewed by the lead author after they observed Child B in a typical school and

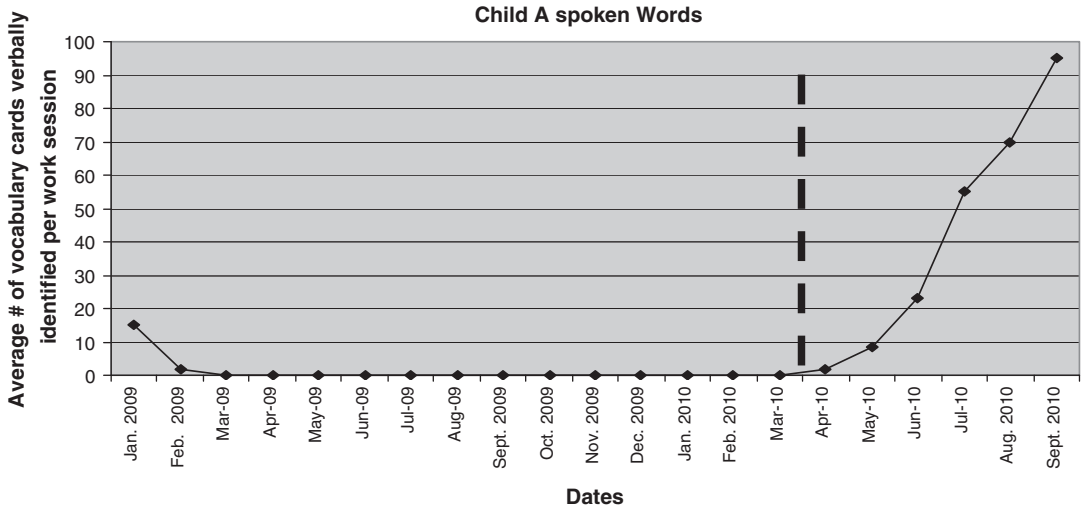

Fig. 4. Parents and teachers collected data of the number of times Child A verbally identified a picture vocabulary card. The data point for each month represents the average for each work session (total correct responses for the month / the number of work sessions). The vertical dotted line represents when antibiotic therapy began.

home setting using the SAP-O form before and after 6 months of antibiotic therapy. Both teachers and parents noted that the only intervention that changed during the 6 month period was the antibiotics. The teachers continued to use the ABA approach and the parents continued their in home interventions the same as before Child B started antibiotics. Parents and teachers could only provide anecdotal data, but they claimed that Child B's hand flapping and toe walking has almost completely resolved. At the time of publication of this paper Child B is still taking antibiotics. Teachers and parents of Child B reported that he continues to show positive progress, but he still meets the criteria for an ASD.

Child C

As of 4/15/2011 Child C is 9 years and 9 months old. The parents of Child C reported a normal child birth with no complications. They claimed that he met all of his developmental milestones, but at age 24 months they noticed strange patterns in his speech. During that same time they noticed that Child C began to become anti social, display restrictive and repetitive behaviors (hand flapping and toe walking) and he became dysregulated frequently. Child C was diagnosed with an ASD (PDD-NOS) at the University of Iowa in February 2005 when he was 4 years and 7 months old (personal communication August 5, 2010).

Child C's inability to sustain eye contact when speaking to another individual is one way he stands out from his neurotypical peers (personal communication March 19, 2011). During a 3 week period (before antibiotic therapy began) baseline data was established to determine how many times he established eye contact with his teacher when he gave a verbal response in the classroom. The teacher recorded twenty trials during the 3 week baseline period where he called on Child C to answer a question in class and Child C gave a verbal response. Each time Child C established eye contact with the teacher he was given credit for a desired response. During the baseline period Child C gave very few desired responses, but after antibiotic therapy began his number of desired responses increased (Fig. 8).

If the increased eye contact that Child C displayed was due to the antibiotic therapy these findings could be noteworthy since marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze is one of the diagnostic criteria of Autism

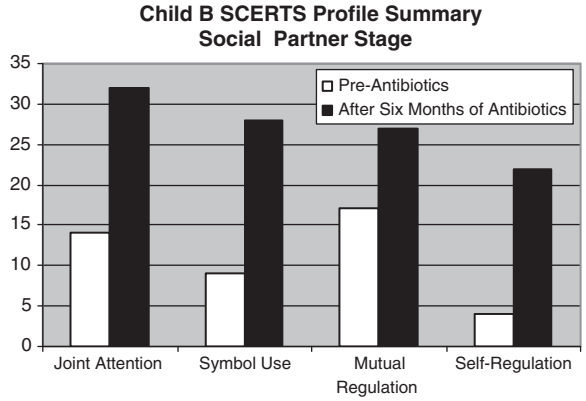

Fig. 7. SCERTS profile summary scores for Child B before antibiotic therapy began and 6 months into antibiotic therapy.

Disorder [4]. Both teachers and parents noted that the only intervention that changed during the 6 month period was the antibiotics (Fig. 9). The teachers continued to use the ABA approach and the parents continued their in home interventions the same as before Child C started antibiotics.

Child D

As of 4/15/2011 Child D is 7 years old. The parents of Child D reported no complications with child birth and claimed that he achieved all of his early developmental milestones. Child D turned towards the sound of a human voice at 3 months, sat up at 4 months, imitated familiar actions at 6 months, crawled at 7 months, walked at 12 months, and said a few words at 12 months. All of these milestones fall under typical social, language, and motor skill development of typical developing children in the first year of life [31].

The parents and teachers of Child D could only provide anecdotal evidence, but they claimed that Child D decreased his repetitive behaviors of hand flapping and toe walking to a point where they have almost completely resolved. If the reduction of toe walking and hand flapping Child D displayed was due to the antibiotic therapy these findings could be noteworthy since stereotyped and

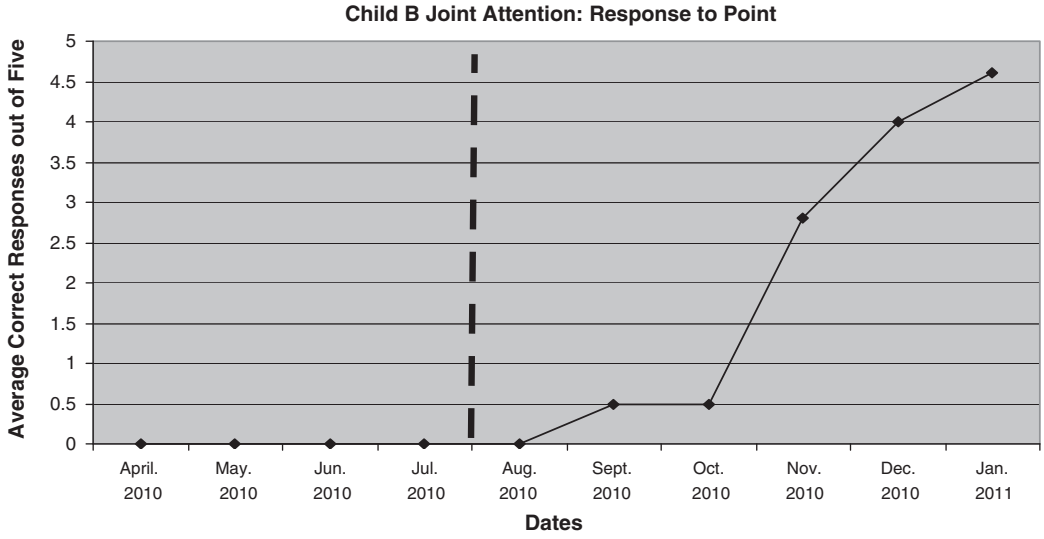

Fig. 6. Teachers pointed to items in the classroom and asked Child B to "look" at the item. When Child B's eye gaze followed the point it was recorded as a correct response. During each work session Child B was asked to follow the teacher's point five times. The data points are the average correct responses per work session per month (total correct responses/number of work sessions). The vertical dotted line represents when antibiotic therapy began.

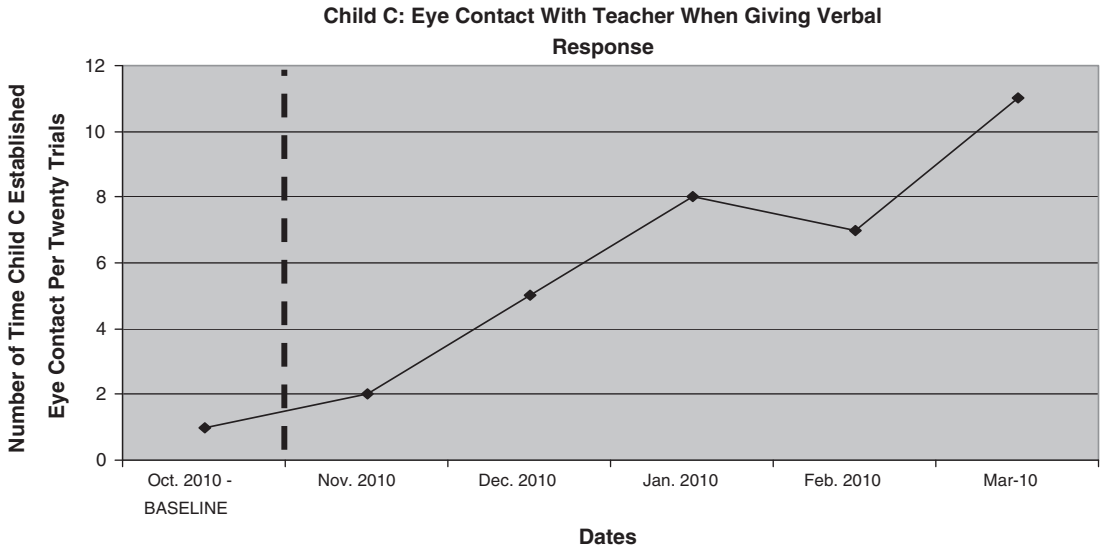

Fig. 8. Number of times Child C gave his teacher eye contact when he responded verbally to a question in his classroom. Twenty trials were collected during the baseline period so for consistency twenty trials were collected during the following months. The vertical dotted line represents when antibiotic therapy began.

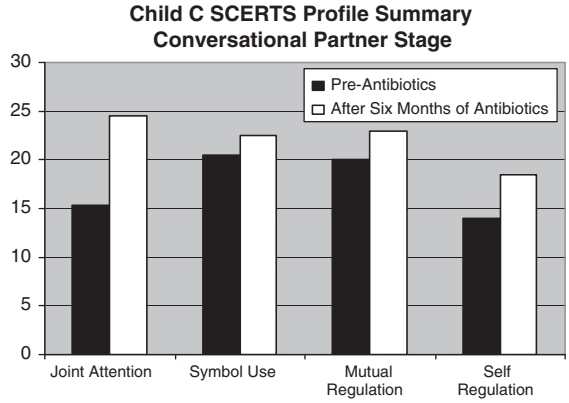

Fig. 9. SCERTS profile summary scores for Child C before antibiotic therapy began and 6 months into antibiotic therapy.

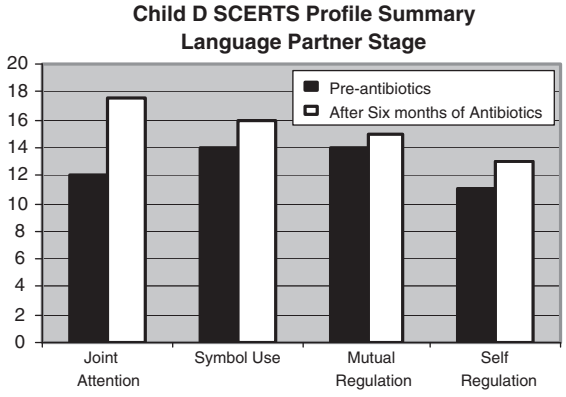

Fig. 10. SCERTS profile summary scores for Child D before antibiotic therapy began and 6 months into antibiotic therapy.

repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements) is one of the diagnostic criteria of Autism Disorder [4].

The parents of Child D reported an increase in verbal communication, a decrease in the repetitive behaviors (humming), and an increase in interactions with siblings and peers (Fig. 10). Both teachers and parents noted that the only intervention that changed during the 6 month period was the antibiotics. The teachers continued to use the ABA approach and the parents continued their in home interventions the same as before Child D started antibiotics. At the time of publication of this paper Child D was still taking antibiotics. He continues to show positive progress but still meets the criteria for an ASD.

Child E

As of 4/15/2011 Child E is 4 years 6 months old. The parents of Child E reported a normal child birth with no complications. He followed a moving person or objects at 3 months, rolled over at 6 months, and smiled at himself in the mirror at 6 months. All of these milestones fall under typical social, language, and motor skill development of typical developing children in the first 6 months of life [31].

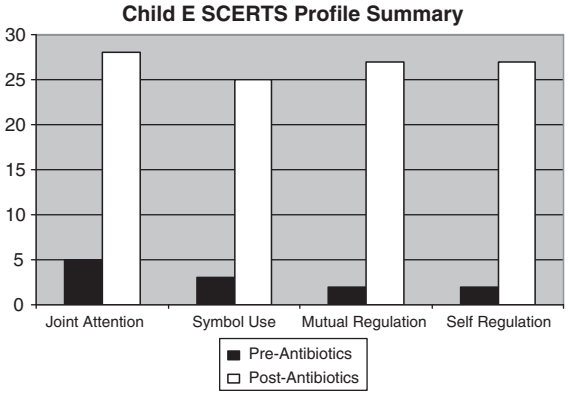

Fig. 11. SCERTS profile summary scores for Child E before antibiotic therapy began and after antibiotic therapy concluded.

The parents of Child E reported that at the age of 9 months he began to show physical symptoms consistent with Lyme disease (Fig. 12). At 18 months they inquired about Lyme disease and after a positive Western Blot blood test they began antibiotic therapy. At that time Child E had not displayed any verbal communication, but

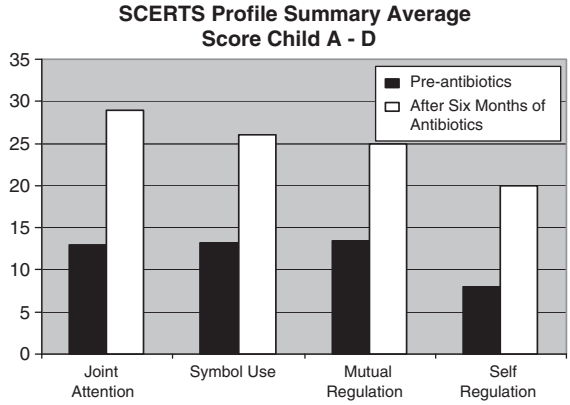

Fig. 12. The average SCERTS profile summary score for Child A–D before they started antibiotics and 6 months later. Child E's scores were not included because his pre-antibiotic score was compared to his score 4 years later after he completed antibiotic therapy.

after 2 weeks of antibiotics he spoke his first word. Parents and teachers reported that he continued to progress and at the end of the 6 month observation period he had developed over one hundred words of speech (Fig. 11).

If the increased verbal communication that Child E displayed was by because of the antibiotic therapy these findings could be significant since delay, or total lack of, the development of spoken language is one of the diagnostic criteria of Autism Disorder [4].

Both teachers and parents noted that the only intervention that changed during the 6 month period was the antibiotics. The teachers continued to use the ABA approach and the parents continued their in home interventions the same as before Child E started antibiotics. At the time of publication of this paper Child E was still taking antibiotics. He continues to show positive progress but still meets the criteria for an ASD.

Consequences of the hypothesis and discussion

All five children in the study showed improvement in their autistic symptomology after beginning long term antibiotic treatment for Lyme disease (Fig. 12). Some of the children showed improvement in verbal communication skills, with Child A regaining his ability communicate after a complete loss of speech after the age of 18 months. That child reportedly began to regain speech ten days after the introduction of antibiotic therapy. Child E also began to acquire speech, signified by speaking his first word ten days after beginning antibiotic therapy.

	Child A	Child B	Child C	Child D	Child E
Age of Diagnosis ASD	26 Months	36 Months	55 Months	36 Months	N/A
Age of Diagnosis LD/Tick Borne Illness	34 Months	42 Months	114 Months	58 Months	18 Months
Physical Symptoms	Loss of previously acquired speech, hand flapping, toe walking, sensitivity to light and sounds, reduced eye contact with peers and parents, and reduced joint attention.	Hand flapping, toe walking, sensitivity to foods and texture, reduced eye contact and joint attention.	Hand flapping, toe walking, sensitivity to texture and sounds, reduced interaction with peers, reduced eye contact with adults and peers, depression, and joint pain	Repetitive behaviors (spinning objects), delayed in speech, reduced eye contact and joint attention.	No acquired speech at 18 months, Sensitivity to light, sounds, and textures, displayed repetitive behaviors, EM rash, insomnia (previously slept through the night), and reduced eye contact.
Positive WB Bands: IgM	23, 31, 34, 39, 41, 45, and 83	31,34,39 and 41	41	31, 34, 41 and 45	23,34,39, and 41
Positive WB Bands: IgG	23,31, 41, and 83	39 and 41	18, 31, 34, 39,41, and 58	31 and 41	39,41, and 58
Co-Infections	Babesiosis, Mycoplasma	None	Babesiosis	Babesiosis	Babesiosis Bartonellosis
Prescribed Antibiotic	Amoxicillin Azithromycin	Amoxicillin Azithromycin	Amoxicillin	Amoxicillin	Amoxicillin Azithromycin
Observed Physical Improvements	Regained ability to speak shortly after starting antibiotics, toe walking and hand flapping resolved, increased eye contact and reciprocal attention.	Hand flapping and toe walking resolved, increased eye contact and reciprocal attention.	Decrease hand flapping and toe walking, increased interaction with peers, increased eye contact and reciprocal attention.	Increase in verbal communication, reduction in repetitive behaviors, increased eye contact and reciprocal attention.	Spoke 1st word, repetitive behaviors resolved, insomnia resolved, increased eye contact and reciprocal attention.

Fig. 13. Age of diagnosis of ASD and LD, physical symptoms, positive WB IgM and IgG bands, co-infections, prescribed antibiotic(s), and physical improvements of the five children in the study.

The parents and teachers of the youngest child in the study reported the most amount of progress during the observation period. The three youngest children in the study (Child A, B, and E) showed the highest increase of mean score on their SCERTS SAP-O form. This raises the potential importance of early screening for Lyme disease as a factor influencing the recovery from infection and changes in the developmental trajectories of children with ASD.

Another interesting similarity all of the children in the study share is that they all displayed "regressive" autism. Regressive autism occurs when a child appears to develop typically but then starts to lose speech and social skills, typically between the ages of 15 and 30 months, and is subsequently diagnosed with autism [35]. The exact etiology of regressive autism is unknown but environmental factors have been suspected [34]. Dr. Brian Fallon has suggested a latency period of months to years between initial infection and onset of symptoms in some patients with neuropsychiatric impairments due to Lyme disease [18]. The parents of the five children in the study could not pinpoint an exact date of infection, but their treating physician suggested that the Bb. bacteria could have been transmitted congenitally since all five of their mothers were diagnosed with Lyme disease (personal communication April 3, 2011) and Bb has been shown to be transmitted congenitally in infected mothers [26]. If the Bb. bacteria were transmitted congenitally and this latency period presented itself in the infected children it could lead to an explanation of their late onset of autistic symptomology.

If the small sample studies are any indication of the number of children who have a diagnosis of an ASD and are infected with Lyme disease there could be a large population of people who could improve their physical and mental health with proper treatment. An estimated 750,000 individuals in the United States are affected by an ASD [12]. If 20% of those individuals test positive for Lyme disease potentially 152,000 people could improve their overall health with antibiotic therapy. More research needs to be conducted to determine if a percentage of children diagnosed with an ASD are experiencing an exacerbation of their ASD symptomology due to Lyme disease.

Dr. Michael Ganz, Assistant Professor of Society, Human Development, and Health at Harvard School of Public Health estimated that the cost to care for an individual with an ASD over their lifetime is 3.2 million dollars [22]. He also estimates that the annual cost to parents and health care providers is between $39,000 and $130,000. If a large number of children can alleviate some of their symptoms with antibiotic therapy to treat their Lyme disease the financial impact could also be significant.

While significant gains were noted in each of the children with ASD (and ASD symptomology) when they received long term antibiotic therapy, it is important to note that there are no claims that the treatment for Lyme disease "cured" the individual of their autism. It is believed that treating the Lyme disease significantly improves the individual's physical and mental health, thereby creating an opportunity for learning, through increased communication skills and social interaction, that had not been present prior to treatment for the physical condition of Lyme disease. It is a reasonable course of action to screen children with ASD for co-occurring Lyme disease and other tick borne illnesses in the case that they are also affected with a debilitating neurological disease and are incapable of effectively communicating poor physical health.

The authors realize that the data from this study is not significant enough to support a definitive claim that long term antibiotic therapy should be a treatment option for children diagnosed with an ASD and Lyme disease. The sample is too small, there is a lack of a control group, and only a single follow up assessment was used. The authors' goal is to disseminate the improvement of the symptomology of Autism Disorder of these five children after long term antibiotic therapy and present a case to hopefully persuade further investigation of the potential exacerbation of autistic symptoms due to Lyme disease infection.

Conflict of interest statement

None of the authors report any conflict of interest.

References

[1] Alaedini A, Latov N. Antibodies against OspA epitopes of *Borrelia burgdorferi* cross-react with neural tissue. J Neuroimmunol 2005;159:192–5.

[2] Adams WV, Rose CD, Eppes SC, Klein JD. Cognitive effects of Lyme disease in children. Pediatrics 1994;94:185–9.

[3] American Autoimmune and Related Disease Association. Autoimmune disorders. Cause, retrieved from: <http://www.aarda.org/>; 2011.

[4] American Psychiatric Association. Pervasive developmental disorders. In: Diagnostic and statistical manual of mental disorders. 4th ed.- text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000. pp. 69–70.

[5] Ashwood P, Wills S, Van de Water J. The immune response in autism: a new frontier for autism research. J Leukoc Biol 2006;80:1–15.

[6] Autism Speaks. Autism Speaks: Science answers, < ,http://www.action.autismspeaks.org/page/content/scienceanswers>; 2010 [retrieved 18.2.2011].

[7] Blumer D, Benson D. Personality changes with frontal and temporal lesions. In: Benson DF, Blumer F, editors. Psychiatric aspects of neurologic disease. New York: Grune & Stratton; 1975.

[8] Bransfeld RC. Lyme disease, comorbid tick-borne diseases, and neuropsychiatric disorders. Psychiatric Times 2007;24:29–32.

[9] Bransfield RC, Wulfman JS, Harvey WT, Usman AI. The association between tick-borne infections, Lyme borreliosis and autism spectrum disorders. Med Hypotheses 2008;70(5):967–74.

[10] Cameron D. Treatment delay as a risk factor for treatment failure in Lyme disease. In: 16th International scientific conferemce on Lyme disease and other tick-borne disorders, Hartford, CT: 2003. [June 7–8 (abstract)].

[11] Centers for Disease Control and Prevention. Lyme disease United States. Morbidity and Mortality Weekly, Report. 2007; 56(23): pp. 573–576.

[12] Centers for Disease Control and Prevention. Autism Spectrum Disorders (ASDs): facts about ASDs, <http://www.cdc.gov/ncbddd/autism/facts.html>; 2010a [retrieved 10.2.2011].

[13] Centers for Disease Control and Prevention. Lyme disease, <http://www.cdc.gov/ncidod/dvbid/lyme/index.htm>; 2010b [retrieved 22.1.2011].

[14] Centers for Disease Control and Prevention. Reported Lyme disease cases by state, 1995–2009, <http://www.cdc.gov/ncidod/dvbid/lyme/ld_rptdLymeCasesbyState.htm>; 2010c [retrieved 25.1.2011].

[15] Comi A, Zimmerman A, Frye V, Law P, Joseph N. Antibodies against OspA epitopes of *Borrelia burgdorferi* familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J Child Neurol 1999;14:388–94. doi:10.1177/088307389901400608.

[16] Dorland's Medical Dictionary for Health. Definition. hypoperfusion, retrieved from <http://www.medical-dictionary.thefreedictionary.com/hypoperfusion>; 2007.

[17] Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology 2007;70(13):922–1003. doi:10.1212/01.WNL.0000284604.61160.2d.

[18] Fallon B, Nields J. Lyme disease: a neuropsychiatric illness. Am J Psychiatry 1994;151(11):1571–83.

[19] Foxx R. Applied behavior analysis treatment of autism: the state of the art. Child and adolescent psychiatric clinics of North America 2008;17(4):821–34.

[20] Gendry Meresse I, Zilbovicius M, Boddaert N, Robel L, Philippe A, Sfaello I, et al. Autism severity and temporal lobe functional abnormalities. Ann Neurol 2005;58(3):466–9.

[21] Hamlen RA, Kilman DS. Lyme disease: etilogy, neuropsychological sequelae, and educational impact. Newspaper of the National Association of School Psychologists 2007;35(5):34–8.

[22] Harvard School of Public Health. Autism has high costs to US Society, retrieved from <http://www.hsph.harvard.edu/news/press-releases/2006-releases/press04252006.html>; 2006.

[23] Helt M, Kelley E, Kinsbourne M, Pandey J, Boorstein H, Herbert M, et al. Can children with autism recover? If so, how? Neuropsychol Rev 2011;18(4):339–66. doi:10.1007/s11065-008-9075-9.

[24] Kolb B, Whishaw I. Fundamentals of human neuropsychology. New York: W.H. Freeman and Co.; 1990.

[25] Logigian EL, Johnson KA, Kijewski MF, Kaplan RF, Becker JA, Jones KJ, et al. Reversible cerebral hypoperfusion in Lyme encephalopathy. Neurology 1997;49:1661–70.

[26] MacDonald AB. Gestational lyme borreliosis. Implications for the fetus. Rheum Dis Clin North Am 1989;15(4):657–77.

[27] Merriam-Webster's Medical Dictionary. Perseveration, <http://www.dictionary.reference.com/browse/perseveration>; 2007 [retrieved 3.3.2011].

[28] National Institute of Allergy and Infectious Disease. Lyme disease: the role of autoimmune reactivity, retrieved from http://www.niaid.nih.gov/topics/lymedisease/research/pages/autoimmune.aspx; 2007.
[29] National Institute of Health. Autoimmune disorders, retrieved from http://www.nlm.nih.gov/medlineplus/ency/article/000816.htm; 2010.
[30] National Institute of Mental Health. Autism Spectrum Disorders: Persuasive Developmental Disorders. (NIH Publication No. 08–5511). Washington, DC: U.S. Government Printing, Office; 2008.
[31] National Network For Child Care. Developmental milestones: A guide for parents, retrieved from http://www.nncc.org/Child.Dev/mile1.html; 1994.
[32] Pachner A. Neurologic manifestations of Lyme Disease, the new "Great Imitator". Clin Infect Dis 1989;11(Suppl. 6):S1482–6 [doi:10.1093]Please provide the full detail of "doi number" for the Ref. [32]..
[33] Prizant BM, Wetherby AM, Rubin E, Amy Laurent C, Rydell PJ. In: Paul H, editor. The SCERTS® model a comprehensive educational approach for children with autism spectrum disorders, Baltimore, MD: Brookes Publishing Co; 2003.
[34] Richler J, Luyster R, Risi S, et al. Is there a 'regressive phenotype' of Autism Spectrum Disorder associated with the measles-mumps-rubella vaccine? a CPEA study. J Autism Dev Disord 2006;36(3):299–316. doi:10.1007/s10803-005-0070-1 [PMID 16729252].
[35] Stefanatos GA. Regression in autistic spectrum disorders. Neuropsychol Rev 2008;18(4):305–19. doi:10.1007/s11065-008-9073-y [PMID].
[36] Strickter R, Lautin A, Burrascano J. Lyme disease: point/counterpoint. Expert Rev Anti Infect Ther 2005; 3(2): doi:10.1586/14787210.3.2.
[37] Thoughtful House For Children. Autism state ranking prevalence, retrieved from <http://www.thoughtfulhouse.org/tech-labs/disabilities/autism-state-rankings-prevalence.php>; 2010.
[38] Vojdani A. Immunology of Lyme disease and associated disorders. LIA Conference 2007.
[39] Zilbovicius M, Boddaert N, Belin P, Poline JB, Remy P, Mangin JF, et al. Temporal lobe dysfunction in childhood autism: a PET study. Positron emission tomography. Am J Psychiatry 2000;157:1988–93.